The maximum alcohol withdrawal syndrome score associates with worse clinical outcomes - A retrospective cohort study

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Abstract: Background: The Wetterling alcohol withdrawal syndrome (AWS) scale determines withdrawal severity and guides treatment. We investigated associations between maximum AWS scores and clinical outcomes. Methods: This retrospective cohort study considered AWS assessments measured from 8/2015-8/2017. We used multivariable linear and logistic regression to analyze associations between the maximum score and increased length of stay (LOS) and in-hospital mortality, respectively. Firstly, we investigated the maximum score of all AWS assessments any time during the stay, secondly, the maximum measured only within the first 3 days of withdrawal. Results: A total of 2,464 hospital stays showed that, patients with “mild” (<6), “moderate” (6–9), and “severe” (>9) maximum scores had median LOS of 5.93, 9.35, 14.71 days, mortality was 1.7%, 4.8%, 8.0%, respectively. Regression showed that a higher maximum score was independently associated with increased LOS and mortality (both $p < 0.001$). Based on the maximum AWS score within the first 3 days, the median LOS was 6.18, 9.00, 12.89 days, mortality was 2.2%, 3.6%, 7.6%, respectively. A higher maximum score in the first 3 days was independently associated with increased LOS ($p = 0.036$) and mortality ($p = 0.001$). Severe maximum AWS scores within 3 days of withdrawal had an odds ratio of 2.53 (95% CI: 1.27, 4.82; $p = 0.0060$) for in-hospital death. Conclusions: Maximum AWS scores associate independently with increased LOS and in-hospital mortality. This association is reproducible within the first 3 days of withdrawal. Development of such a 3-day tool could help clinicians assess the risk of worse clinical outcomes early on and adjust care accordingly.

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The Maximum Alcohol Withdrawal Syndrome Score Associates with Worse Clinical Outcomes – A Retrospective Cohort Study

Running title
High Maximum AWS Score Indicates Worse Outcomes

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Abstract

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Results: A total of 2,464 hospital stays showed that, patients with "mild" (<6), "moderate" (6-9), and "severe" (>9) maximum scores had median LOS of 5.93, 9.35, 14.71 days, mortality was 1.7%, 4.8%, 8.0%, respectively. Regression showed that a higher maximum score was independently associated with increased LOS and mortality (both $p<0.001$).

Based on the maximum AWS score within the first 3 days, the median LOS was 6.18, 9.00, 12.89 days, mortality was 2.2%, 3.6%, 7.6%, respectively. A higher maximum score in the first 3 days was independently associated with increased LOS ($p=0.036$) and mortality ($p=0.001$). Severe maximum AWS scores within 3 days of withdrawal had an odds ratio of 2.53 (95% CI: 1.27, 4.82; $p=0.0060$) for in-hospital death.

Conclusions: Maximum AWS scores associate independently with increased LOS and in-hospital mortality. This association is reproducible within the first 3 days of withdrawal. Development of such a 3-day tool could help clinicians assess the risk of worse clinical outcomes early on and adjust care accordingly.

Keywords

- Alcohol withdrawal syndrome (AWS)
- Alcohol use disorder (AUD)
- Wetterling scale (AWS scale)
- In-hospital mortality
- Length of stay (LOS)
- Multimorbidity

1. Introduction

Alcohol Use disorder (AUD) is a diagnosis given to patients who drink excessive amounts of alcohol over longer periods of time leading to cravings, physical and mental health problems, social maladaptation, poor medication adherence, loss of productivity, economic loss and psychiatric comorbidity (Grant et al., 2015; Hasin et al., 2007). Consumption of more than 100 g/week (5-6 glasses of wine) alcohol is associated with many subtypes of cardiovascular diseases, such as stroke, coronary disease and heart failure, and with an increased risk of all-cause mortality (Wood et al., 2018). It is reported that up to 40% of hospitalized patients as well as up to one third of patients being admitted to ICU suffer from this disorder (de Wit et al., 2010). Management of this disorder includes withdrawal and then lifelong abstinence or reduction of consumption (Litten et al., 2016).

Alcohol withdrawal syndrome (AWS) occurs when abruptly terminating alcohol consumption (Jesse et al., 2017). Symptoms of AWS include anxiety, agitation, tremors, insomnia, tachycardia, hypertension, and in severe cases hallucinations, confusions, seizures and cardiac arrhythmias (Wetterling et al., 2006), in which the gold standard of treatment is Benzodiazepines (Sachdeva et al., 2015). Symptoms of AWS need to be monitored to assess AWS severity and guide treatment. One instrument facilitating such assessments is the *Wetterling AWS scale* (Wetterling et al., 1997), a validated scale (Williams, 2001).

Research on AWS is often overshadowed by the focus of public health (Room et al., 2005) on the epidemiology of alcohol use and its prevention (Axley et al., 2019). The limited prior literature has identified clinical variables contributing to AWS severity such as injury severity, hypokalemia and delirium tremens (Moore et al., 2017). AWS is known to be associated with worse clinical outcomes (Monte et al., 2010) and it substantially increases the length of stay (LOS) (Jesse et al., 2017; Salottolo et al., 2017). Factors determining AWS

survival include the number of comorbidities and clinical manifestation (Monte et al., 2010). Patients who suffer multiple withdrawals and relapses are known to go through a process called kindling, in which there is progressive worsening of symptoms with each detoxification (Modesto-Lowe et al., 2005). Most publications on AWS, however, do not consider important confounders such as traumatic injuries, cirrhosis or differential diagnostics in their analysis. Further confusion arises from a variety of different, sometimes unreliable and invalidated, AWS assessment scales (Williams, 2001), obstructing standardized and cooperative research.

To the best of our knowledge, no study has investigated alcohol withdrawal with a large sample size in the context of the clinical meaning of the *maximum* Wetterling AWS score. We therefore analyzed whether the maximum AWS score associates with worse clinical outcomes, in particular the LOS and in-hospital mortality.

2. Methods

2.1 Design, setting and study period

This retrospective cohort study was conducted at the University Hospital Zurich, a tertiary care academic medical center, which has approximately 850 beds and around 40,000 hospital stays a year. Our dataset was derived from electronic health records (EHR), i.e., routinely and prospectively collected data. The electronic version of the Wetterling AWS scale was introduced at our institution in 08/2015, thus all records from this time point on through to 08/2017 were considered.

The investigation used completely anonymous data and conforms to both local law as well as the ethical review and research policies of the University Hospital Zurich. Our study adhered to STROBE guidelines (STrengthening the Reporting of OBservational studies in Epidemiology) (von Elm et al., 2007).

2.2 Population

We included all inpatients, aged ≥18, hospitalized in any clinical unit, who had undergone at least one AWS assessment with a respective entry in their EHR.

2.3 Wetterling Scale

The Wetterling Scale (Wetterling et al., 1997) is an 11-item scale in which somatic features (pulse rate, diastolic blood pressure, temperature, breathing rate, sweating, and tremor) and mental features (agitation, contact, orientation, hallucinations, and anxiety) are assessed to make the AWS quantifiable. It was developed by exclusively taking variables from the CIWA (Clinical Institute Withdrawal Assessment for Alcohol) scale with a Cronbach's $\alpha > 0.8$ (Williams, 2001). The inter-rater reliability (κ value) for the scale was determined as 0.64. The authors emphasized the easy administration for trained personnel (Wetterling et al., 1997). Of

note, the Wetterling Scale is one of the few validated scales which also includes blood pressure, pulse and temperature, not only for the overall assessment, but also in the scale itself (Williams, 2001).

2.4 AWS assessments

Our hospital is an alcohol-free institution and does not serve patients alcoholic beverages during their stay. AWS assessments are performed by nurses per the institution's Standard Operating Procedures if AUD is suspected and diagnosed. AUD is diagnosed by means of the CAGE questionnaire (Ewing, 1984) within 24h of admission, under consideration of the medical history, laboratory tests and the diagnosis list.

One AWS assessment usually takes less than 15 minutes. AUD Patients can have multiple assessments, depending on changes in their condition and symptom severity. The minimum is one assessment per day in patients with very mild AWS.

Nurses are trained in the assessment methodology and in the recording of the vegetative and psychological symptoms (suggestive questioning). The AWS assessment is always accompanied by a Delirium Observation Scale (DOS) assessment (Boettger et al., 2017), which helps physicians and nurses better capture mental symptoms. All those processes are standardized. In this study, the beginning of withdrawal was defined as the time point of the first AWS assessment.

2.5 Outcomes and measures

We analyzed potential associations of the maximum AWS score with worse clinical outcomes, i.e., increased LOS and in-hospital mortality, using multivariable linear and logistic regression, respectively.

- As a first step, we included all AWS scores over the entire course of the hospital stay. However, we only considered the highest AWS value measured during a patient's stay, which was the *maximum AWS score* per definition.
- For the second step, we restricted the AWS values to those assessed within the first three days of withdrawal, beginning with the first assessment. We considered the highest measured value in this three-day period only. Associations with such a "three-day maximum AWS score" could be helpful to clinical decision making.

2.6 Exposure

The exposure of interest was the maximum measured AWS score per patient stay. The AWS scale measures vegetative and psychopathological symptoms. Vegetative symptoms include pulse rate, diastolic blood pressure, temperature, respiratory rate, sweating, and tremor. The mental symptoms include agitation, anxiety, tactile disturbance, disorientation, and hallucinations. Each of these symptoms contribute to the AWS assessment scale, leading to different scores and an increasing severity of the AWS (Jesse et al., 2017). In our main analyses, we considered the maximum score as a continuous variable.

The scores are categorized into "mild" (<6), "moderate" (6-9), and "severe" (>9) AWS states (Wetterling et al., 1997). By using this categorization, we stratified patient characteristics and illustrated the strength of associations of maximum AWS scores according to their severity categories in secondary analyses.

2.7 Co-variables

Co-variables were selected based on a prior knowledge and the medical literature (Jesse et al., 2017). We adjusted for age, sex, marital status, pneumonia (ICD-10 diagnosis codes J13*-J18* [International Classification of Diseases, WHO, Geneva, Switzerland; asterisk means zero or more digits]), hyponatremia (E87.1), head injuries (S00*-S02*, S06*-S09*), depression, chronic heart failure, chronic pain, decompensated liver cirrhosis and diabetes (Tonelli et al., 2015). We additionally controlled for general multimorbidity severity by adjusting for the number of diagnoses (Sharabiani et al., 2012), since the maximum AWS score measured tended to be higher in patients with higher diagnosis counts, which had similarly been reported about in its predecessor, the CIWA scale (Duby et al., 2014).

2.8 Data processing and statistical analysis

Routinely and prospectively collected EHR data were extracted from the clinical data warehouse, exported to raw data files, which in turn were imported into a separate database management. We used structured query language (SQL) statements to manage that database as well as to process the data so that only minor data processing steps were necessary during statistical analysis.

The AWS severity categories were used to stratify patient characteristics. Moreover, we additionally stratified the data by sex (Supplementary Table ST1[2]) as recommended (Institute of Medicine (US) Committee on Women's Health Research, 2010).

Comparative statistical analysis was performed to describe patient characteristics according to their maximum AWS score severity category. We used Kruskal-Wallis tests to compare the distributions of continuous variables between groups and Fisher's exact tests to compare categorical variables.

We computed adjusted multivariable linear and logistic regression models to analyze potential associations of the maximum AWS score with increased LOS and in-hospital mortality, respectively.

We conducted all tests as 2-sided and determined p-values of ≤ 0.05 to be indicative for statistical significance. Statistical analyses were performed using the software R, version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Overall, a total of 2,464 hospital stays with 19,312 AWS assessments were included (Figure 1).

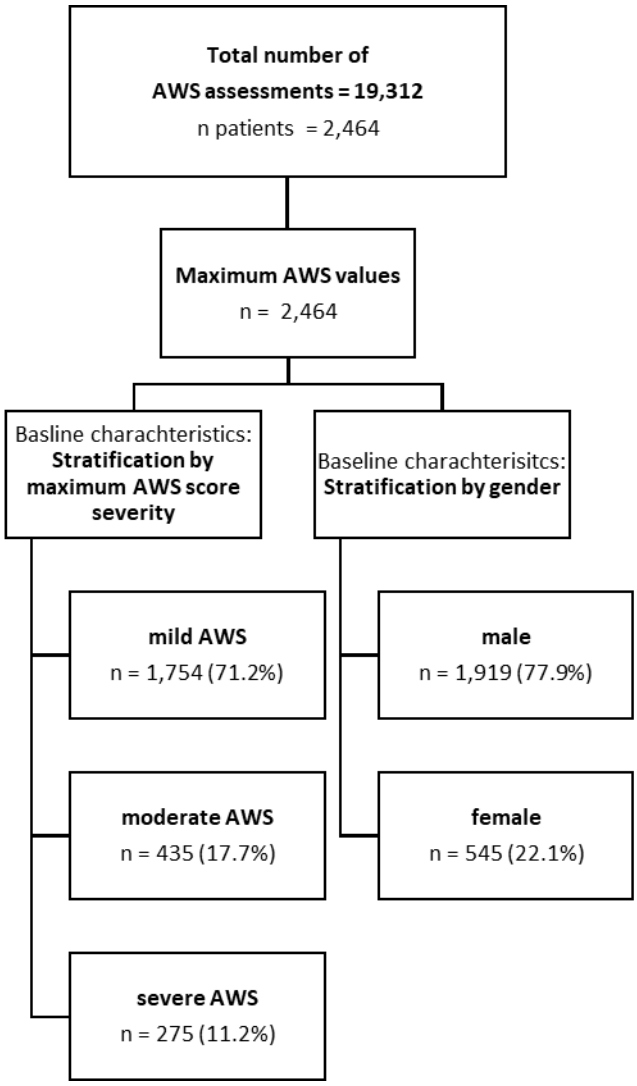

Figure 1. Study flow diagram.

Considering only the first AWS assessment per hospital stay, 82.2% of first assessments were performed within three days after admission into hospital care (878 stays had their first assessment on day one; 881 stays on day two; 267 stays on day three; 438 stays on day four or later). The median for the first assessment was day 2 (IQR: 1, 3). Of the first measured AWS

scores (median: 2; IQR: 0, 4), 2,036 ranked as mild (82.6%), 322 as moderate (13.0%) and 106 (5.2%) as severe.

The median maximum AWS score was 3 (IQR: 1, 6) and was usually reached on the third day (median: 3 IQR: 2, 5). Stratification by maximum AWS score resulted in 1,754 mild cases (71.2%), 435 moderate cases (17.7%), and 275 severe cases (11.2%). Detailed patient characteristics are shown in Table 1.

Table 1 Baseline characteristics mild, moderate and severe AWS maximum score (AWS stays n = 2,464)

Variable	mild	moderate	severe	p
n° (%)	1754 (71.1)	435 (17.6)	275 (11.1)	
Age (median, IQR)	61.00 [50.00, 70.00]	61.00 [51.00, 71.00]	59.00 [50.00, 70.00]	0.756
BMI (mean, SD)	25.59 (14.58)	26.89 (20.66)	25.00 (4.49)	0.496
Sex (n, %)				
Male	1359 (77.4)	334 (76.7)	226 (82.1)	0.171
Female	395 (22.5)	101 (23.2)	49 (17.8)	
Marital status (n, %)				
married/partner	631(36.0)	141(32.4)	82 (29.8)	
Single	557 (31.8)	136 (31.3)	97 (35.3)	0.111
widowed/divorced/separated	465 (26.5)	131 (30.1)	71 (25.8)	
unknown/other	101(5.8)	27 (6.2)	25 (9.1)	
Died during Stay (n, %)	29 (1.7)	21 (4.8)	22 (8.0)	<0.001
LOS (median, IQR)	5.93 [2.91,11.11]	9.35 [4.88, 17.30]	14.71 [7.47, 23.72]	<0.001
AWS (median, IQR)	3.00 [1.00, 4.00]	7.00 [6.00, 8.00]	12.00 [11.00, 15.00]	<0.001
BAC (median, IQR)	50.65 [34.88, 68.03]	47.80 [30.80, 66.60]	51.60 [26.40, 70.14]	0.772
Alcohol level in permille (median, IQR)	2.30 [1.60, 3.10]	2.20 [1.40, 3.10]	2.40 [1.30, 3.20]	0.799
n° Diagnosis (median, IQR)	7.00 [4.00, 10.00]	9.00 [6.00, 14.00]	12.00 [8.00, 18.00]	<0.001
Pneumonia (n, %)	54 (3.1)	31 (7.1)	27 (9.8)	<0.001
Hyponatremia (n, %)	88 (5.0)	35 (8.0)	28 (10.2)	0.001
Head injuries (n, %)	313 (17.8)	69 (15.9)	53 (19.3)	0.471
Depression (n, %)	181 (10.3)	48 (11.0)	30 (10.9)	0.865
Chronic Heart Failure (n, %)	80 (4.6)	38 (8.7)	29 (10.5)	<0.001
Chronic Pain (n, %)	74 (4.2)	16 (3.7)	7 (2.5)	0.421
Diabetes (n, %)	204 (11.6)	56 (12.9)	31 (11.3)	0.727
CPD (n, %)	153 (8.7)	42 (9.7)	29 (10.5)	0.531
Cirrhosis (n, %)	123 (7.0)	38 (8.7)	42 (15.3)	<0.001
ALT (median, IQR)	21.00 [14.00, 34.00]	20.00 [13.00, 47.25]	21.00 [13.00, 40.00]	0.691
AST (median, IQR)	28.00 [21.00, 48.00]	33.00 [21.00, 101.00]	37.00 [23.50, 105.00]	<0.001
GGT (median, IQR)	72.00 [31.00, 155.75]	104.00 [37.00,182.25]	112.00 [43.00,182.00]	<0.001

BMI = body mass index; LOS = length of stay; CPD = Chronic pulmonary disease; ALT = alanine-aminotransferase; AST = aspartate aminotransferase; GGT = Gamma-Glutamyl transferase;
n BMI = 1042 ; n Died during stay = 72 ; n BAC = 428 ; n Alcohol level in permille = 412 ; n pneumonia = 112 ; n hyponatremia = 151 ; n head injuries = 435; n depression = 259 ; n chronic heart failure = 147 ; n chronic pain = 97
n diabetes = 291 ; n CPD = 224 ; n cirrhosis = 203 ; n ALT = 2008 ; n AST = 1751 ; n GGT = 1618

Figure 2 illustrates that patients with multiple diagnoses had higher maximum AWS scores compared to those patients with only few diagnoses. In other words, multimorbid patients were at risk for higher maximum AWS scores. It was therefore important that our regression models additionally controlled for the number of diagnoses.

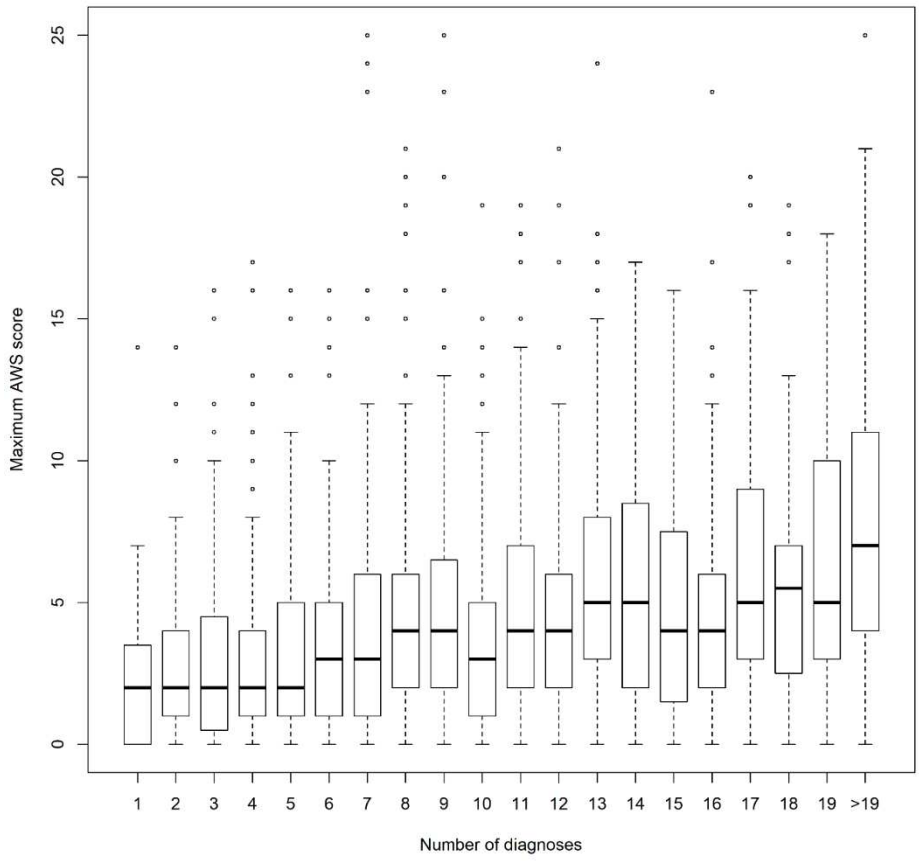

Figure 2. This figure illustrates that patients with multiple diagnoses (right-hand side) showed higher maximum AWS scores compared to those patients with only few diagnoses (left-hand side). In other words, multimorbid patients were at risk for higher maximum AWS scores. It was therefore important that our regression models additionally controlled for the number of diagnoses.

Maximum AWS score, LOS and death

Patients with mild, moderate, and severe maximum AWS scores had a median LOS of 5.93, 9.35, 14.71 days, and 1.7%, 4.8%, 8.0% patients died during their stay, respectively.

Multivariable regression showed that this was independent of other variables entered into the model (Table 2).

When using the severity groups instead of the continuous variable, the same analysis resulted in an increased LOS of 1.41 days (95% confidence interval [CI]: 0.49, 2.33; p=0.0027) and 2.53 days (95% CI: 1.39, 3.67; p<0.001) for moderate and severe AWS according to the maximum score, respectively. The odds ratios for in-hospital mortality were 2.17 (95% CI: 1.15, 4.00; p=0.015) and 3.17 (95% CI: 1.65, 6.00; p<0.001) for moderate and severe maximum scores, respectively.

Table 2 Multivariable regression models for LOS and in-hospital mortality considering the continuous variable of the maximum AWS score during the entire hospital stay.

		LOS			**in-hospital mortality**	
variable	estimate	CI	p value	OR	CI	p value
Maximum AWS score	0.271	0.184 ; 0.358	< 0.001	1.098	1.044 ; 1.152	< 0.001
Age	-0.003	-0.030 ; 0.024	0.830	1.056	1.032 ; 1.082	< 0.001
Sex	0.127	-0.703 ; 0.958	0.764	0.920	0.477 ; 1.679	0.793
Marital status						
other/unknown	-1.126	-2.611 ; 0.360	0.138	1.035	0.325 ; 2.715	0.948
single	-0.462	-1.356 ; 0.432	0.311	0.963	0.467 ; 1.927	0.917
widowed/divorced/separated	-0.865	-1.745 ; 0.014	0.054	1.289	0.703 ; 2.350	0.408
number of Diagnoses	1.136	1.066 ; 1.205	< 0.001	1.074	1.037 ; 1.112	< 0.001
Pneumonia	4.236	2.488 ; 5.984	< 0.001	1.191	0.520 ; 2.545	0.665
Hyponatremia	-1.083	-2.529 ; 0.363	0.142	1.119	0.476 ; 2.377	0.783
Head injuries	-4.515	-5.432 ; -3.598	< 0.001	0.513	0.205 ; 1.120	0.122
Depression	-1.090	-2.214 ; 0.035	0.058	0.936	0.363 ; 2.080	0.880
Chronic heart failure	-1.196	-2.731 ; 0.339	0.127	0.868	0.380 ; 1.844	0.724
Chronic Pain	-0.754	-2.511 ; 1.003	0.400	3.117	1.244 ; 6.946	< 0.001
Cirrhosis	-0.042	-1.398 ; 1.314	0.952	4.407	2.220 ; 8.623	< 0.001
Diabetes	-1.321	-2.408 ; -0.235	0.017	0.935	0.464 ; 1.772	0.842

CI = confidence interval, OR = Odds Ratio

Maximum AWS score within the first three days of withdrawal, LOS and death

The maximum AWS scores within the first three days of withdrawal were considered. Patients with mild, moderate, and severe maximum AWS scores within the first three days of withdrawal had a median LOS of 6.18, 9.00, 12.89 days, and 2.2%, 3.6%, 7.6% died over the

course of the hospitalization, respectively. Again, a higher maximum AWS score within the first 3 days of withdrawal was independently associated with increased LOS and mortality (Table 3).

Using the severity groups instead of the continuous variable, the same methods of analysis resulted in statistically insignificant increases of the LOS by 0.23 days (95% CI: -0.72, 1.19; p=0.63) and 0.78 days (95% CI: -0.45, 2.01; p=0.21) for moderate and severe AWS, respectively. While the odds ratio for in-hospital mortality was 1.22 (95% CI: 0.61, 2.33; p=0.55) for moderate maximum AWS scores, we found that a severe maximum AWS score had an increased odds ratio of 2.53 (95% CI: 1.27, 4.82; p=0.0060) for in-hospital death when assessed within the first three days of withdrawal.

Table 3 Multivariable regression models for the outcomes LOS and in-hospital mortality, analyzing the independent association with the continuous variable of the maximum AWS score assessed within the first three days of withdrawal.

		LOS			**in-hospital mortality**	
variable	estimate	CI	p value	OR	CI	p value
Maximum AWS score in first 3 days	0.098	0.006 ; 0.190	0.036	1.095	1.036 ; 1.155	0.001
Age	-0.005	-0.032 ; 0.022	0.720	1.056	1.032 ; 1.082	< 0.001
Sex	0.074	-0.762 ; 0.90	0.863	0.913	0.473 ; 1.668	0.776
Marital status						
other/unknown	-0.970	-2.466 ; 0.523	0.204	1.041	0.326 ; 2.738	0.939
single	-0.378	-1.277 ; 0.522	0.411	1.011	0.491 ; 2.017	0.976
widowed/divorced/separated	-0.820	-1.706 ; 0.066	0.070	1.268	0.692 ; 2.301	0.438
number of Diagnoses	1.180	1.112 ; 1.249	< 0.001	1.079	1.043 ; 1.117	< 0.001
Pneumonia	4.201	2.442 ; 5.961	< 0.001	1.108	0.478 ; 2.397	0.802
Hyponatremia	-0.956	-2.412 ; 0.499	0.198	1.170	0.498 ; 2.486	0.700
Head injuries	-4.604	-5.527 ; -3.682	< 0.001	0.503	0.199 ; 1.094	0.109
Depression	-1.144	-2.276 ; -0.012	0.048	0.881	0.340 ; 1.967	0.775
Chronic heart failure	-1.273	-2.818 ; 0.273	0.106	0.839	0.367 ; 1.781	0.661
Chronic Pain	-0.982	-2.750 ; 0.787	0.277	3.059	1.225 ; 6.800	< 0.001
Cirrhosis	-0.120	-1.487 ; 1.246	0.863	4.12	2.326 ; 9.007	< 0.001
Diabetes	-1.480	-2.574 ; -0.387	0.008	0.908	0.452 ; 1.718	0.777

CI = confidence interval, OR = Odds Ratio

4. Discussion

In this study, we found that the maximum AWS score was independently associated with increased LOS and in-hospital mortality. We used adjusted multivariable linear and logistic regression models to analyze potential associations between the maximum AWS scores and these clinical outcomes. These findings were also found to be reproducible when considering only the first three days after start of alcohol withdrawal. Furthermore, a severe AWS score (10 or higher) measured within the first three days of withdrawal was statistically significantly associated with a 2½-fold increase in the odds of in-hospital death.

Alcohol withdrawal begins within several hours after the last alcohol intake depending on the severity of the AUD. The most serious symptoms can peak at 24 hours or prolong up to several days after the last consumption (Stobart Gallagher and Gomez, 2018)**.** Our study shows that higher AWS scores associate with increased mortality as AWS is known to be linked with worse clinical outcomes (Monte et al., 2010; Salottolo et al., 2017). As corroborated by our results, severe AWS is associated with symptoms, which may occur several days after the beginning of withdrawal, such as delirium tremens (Moore et al., 2017) and increases the patients' LOS (Jesse et al., 2017).

Alcohol (ethanol) is a central nervous system depressant, which triggers an adaptive process and the molecular changes associated with tolerance leading to imbalance of excitation and inhibition (Olsen and Spigelman, 2012). This molecular change in network leads to a wide range of complications, such as a neuroexcitatory effect, that plays an important role in AWS and may contribute to increased LOS and mortality (Connor et al., 2016; Hammond et al., 2017).

Patients with AUD may be overseen in the initial screening process, as CAGE has been criticized for its inability to detect AUD in some age groups (Larimer and Cronce, 2002). This may lead to delayed treatment of patients with AWS and worse clinical outcomes. Furthermore,

it may be difficult to identify AWS patients with comorbidities mimicking AWS, potentially leading to delayed diagnosis and worse outcomes.

Our results show a substantial increase of aspartate transaminase (AST) and gamma-glutamyltransferase (GGT) liver values found in patients with greater AWS severity classification, corroborating previous findings (Botros and Sikaris, 2013). The change in the aspartate transaminase/alanine transaminase ratio (AST/ALT ratio) and GGT values are indicators for severe liver damage, which was confirmed by a substantially increased number of patients with cirrhosis in the higher AWS categories (Botros and Sikaris, 2013). AST, ALT, GGT markers are easily measured and inexpensive, but their predictive value is limited due to low specificity (Jesse et al., 2017). Alcoholic cardiomyopathy is a common diagnosis found among chronic alcoholics and may explain the increased proportion of chronic heart failure in patients with greater AWS severity classification (Guzzo-Merello et al., 2014). The rate of morbidity due to infections, cardiopulmonary insufficiency and bleeding disorders is known to be greater in chronic alcoholics (Maldonado et al., 2015).

Our study supports the introduction and routine use of the Wetterling AWS scale in hospital settings in a standardized manner. We used routinely prospectively collected EHR data to investigate a large cohort of inpatients undergoing alcohol withdrawal, analyzing nearly 20,000 AWS assessments, after its implementation in 2015. No stays were excluded if the patient had at least one valid AWS assessment, increasing the generalizability of our study. The Wetterling AWS score assessments do not account for multimorbidity, which may bias the AWS assessment results. Future studies should therefore consider comorbidities and the number of diagnoses a patient has. Patients with comorbidities and/or higher diagnosis counts may present higher unwarranted AWS scores and it is yet to be tested if this lack of consideration may lead to suboptimal treatment. The predecessor of the AWS scale, the CIWA scale, was found to confound with comorbidities such as trauma and critical illnesses (Duby et

al., 2014). Based on our findings that the maximum AWS score tends to increase with diagnosis count and appears to be subjected to the same limitation as CIWA (Figure 2.). We therefore used adjusted regression models, controlling for age, sex, marital status, diagnosis count and important comorbidities.

This study has several strengths. We considered a large sample of hospital stays and AWS assessments. The *maximum* AWS score is an innovative marker indicating worse clinical outcomes. The Wetterling scale is a validated scale for AWS (Williams, 2001). The findings of this study can be adapted to different clinical settings and translated to benefit practitioners and guide future treatment. We believe our findings will contribute to the still limited literature concerning AWS and be a first step towards more effective and personalized patient treatment.

However, the limitations of the study need to be taken into account when interpreting our results. This was a single center study. While we did conduct retrospective analyses of EHR data, these data were still routinely and prospectively collected. Our definition of the comorbidities was based on ICD-10 codes added by professional coders to the diagnosis lists after the patients are discharged. This coding procedure does not allow for analysis of changes over time of severity of comorbidities during hospital stay. And whereas we had data on only the final score result per AWS assessment, there was no information available on the different vegetative and psychopathological subcategories of the Wetterling assessment.

We found that the introduction of a 3-day timeframe for the considerations of the maximum scores measured within this period, was sufficient to show associations with increased LOS and in-hospital mortality independent of the remaining AWS assessments. These maximum AWS values within three days of withdrawal may help health care providers to adjust their treatment and to anticipate AWS progression.

Considerations for future studies include validations of our results and prospective evaluations. In this context, an electronic reminder could automatically calculate the maximum

AWS score after a timeframe of three days starting with the first AWS score entry, and studies could investigate the value of predictive abilities of such clinical decision support. Whether the associations identified in this work are transferable to other AWS assessment scales or other unrelated assessments, e.g. delirium scores, are further unanswered questions that could be addressed.

In summary, the data derived from our large cohort were in line with the literature, and importantly, maximum AWS scores were associated with worse clinical outcomes in terms of LOS and mortality.

5. Conclusions

Higher maximum AWS scores are associated with increased LOS and in-hospital mortality. Determination of the maximum AWS score within 3 days after the first assessment appears to be sufficient and may predict increased LOS and in-hospital mortality. This may help health care providers to anticipate AWS progression and in properly preparing short-, medium-, and long-term care.

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Competing interests statement

The authors have no competing interests.

Contributorship statement

PEB conceived and designed this study. ANG processed the data and performed the statistical analyses. ANG, BUM, EB, and PEB interpreted data. ANG and PEB drafted the manuscript with BUM and EB reviewing and critically commenting on all draft versions. All authors approved the final submitted version of the manuscript.

Ethics approval

The present investigation used completely anonymous data and conformed with local law as well as the ethical review and research policies of the University Hospital Zurich.

Highlights

- Maximum alcohol withdrawal syndrome (AWS) score is higher in multimorbid patients.
- Higher maximum AWS scores associate with worse outcomes (length of stay/mortality).
- Those findings are reproducible already within the first 3 days of withdrawal.
- Such a 3-day tool may help to assess risk and adjust patient treatment early on.

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Supplementary online material [3]

Supplementary Table ST1 Baseline characteristics stratified by sex (AWS stays n = 2,464)

Variable	male	female	p
n (%)	1919 (77.8)	545 (22.1)	
BMI (mean, SD)	25.92 (11.04)	25.28 (24.31)	0.569
Age (median, IQR)	60.00 [50.00,71.00]	61.00 [51.00, 70.00]	0.355
Marital status (n, %)			
married/partner	712 (37.1)	142 (26.1)	<0.001
single	628 (32.6)	162 (29.6)	
widowed/divorced/separated	452 (23.7)	215 (39.4)	
unknown/other	127 (6.6)	26 (4.8)	
Died during Stay (n, %)	57 (3.0)	15 (2.8)	0.886
LOS (median, IQR)	6.97 [3.17, 13.68]	7.09 [3.37, 13.54]	0.679
AWS (median, IQR)	3.00 [1.00, 6.00]	3.00 [1.00, 6.00]	0.514
Mild (n, %)	1359 (70.8)	395 (72.5)	
Moderate (n, %)	334 (17.4)	101 (18.5)	0.177
Severe (n, %)	226 (11.8)	49 (9.0)	
BAC (median, IQR)	50.20 [30.83, 67.60]	53.30 [34.10, 71.50]	0.769
Alcohol level in permille (median, IQR)	2.30 [1.50, 3.10]	2.50 [1.60, 3.25]	0.824
n Diagnosis (median, IQR)	8.00 [5.00, 12.00]	8.00 [5.00, 12.00]	0.371
Pneumonia (n, %)	90 (4.7)	22 (4.0)	0.562
Hyponatremia (n, %)	107 (5.6)	44 (8.1)	0.042
Head injuries (n, %)	329 (17.1)	106 (19.4)	0.226
Depression (n, %)	172 (9.0)	87 (16.0)	<0.001
Chronic Heart Failure (n, %)	117 (6.1)	30 (5.5)	0.682
Chronic Pain (n, %)	71 (3.7)	26 (4.8)	0.262
Diabetes (n, %)	247 (12.9)	44 (8.1)	0.002
CPD (n, %)	174 (9.1)	50 (9.2)	0.867
Cirrhosis (n, %)	157 (8.2)	46 (8.4)	0.726
ALT (median, IQR)	22.00 [14.00, 39.00]	19.00 [13.00, 29.00]	<0.001
AST (median, IQR)	30.00 [21.00, 64.00]	29.00 [20.00, 51.00]	0.056
GGT (median, IQR)	100.50 [35.00,167.25]	69.00 [27.00, 155.00]	0.002

BMI = body mass index; LOS = length of stay; CPD = Chronic pulmonary disease; ALT = alanine-aminotransferase; AST = aspartate aminotransferase; GGT = Gamma-Glutamyl transferase;
n BMI = 1042 ; n Died during stay = 72 ; n BAC = 428 ; n Alcohol level in permille = 412 ; n pneumonia = 112 ; n hyponatremia = 151 ; n head injuries = 435; n depression = 259 ; n chronic heart failure = 147 ; n chronic pain = 97
n Diabetes = 291 ; n CPD = 224 ; n cirrhosis = 203 ; n ALT = 2008 ; n AST = 1751 ; n GGT = 1618